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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,614	03/01/2000	GAIL PETUNA RISBRIDGER	229752000800	6186

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EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,614	RISBRIDGER ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,40-63 and 68* is/are pending in the application.

4a) Of the above claim(s) *1-26,40-57 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,60,62,63 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Risbridger *et al.*

Date of priority: 04/23/1997

Request for Continued Examination

The request filed on 01/07/2004 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/402,614 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 58, 60, 62, 63, and 68 are currently under consideration.

New Rejections/Objections:

Claim Objections

Claim 63 is objected to for reciting "The method according to claim 61.." as it appears that the status of claim 61 is currently "withdrawn".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58, 60, 62, 63, and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of screening a mammal having prostate cancer or predisposition to prostate cancer comprising screening for modifications to inhibin protein levels, including various isoforms of said inhibin.

With regards to an inhibin, the specification teaches (page 3) that reference to "inhibin" should be read as including reference to 11 forms of inhibin and fragments thereof or derivatives, homologues, analogues, mutants and variants thereof including all subunit polypeptides thereof including by way of example any protein encoded by the α or β subunit gene, the monomeric α-subunit polypeptide, the subunit precursor polypeptides pre, pro αN and αC, the monomeric β subunit polypeptide, the dimeric αβ polypeptide (for example $\alpha\beta_A$, $\alpha\beta_B$, $\alpha\beta_C$, $\alpha\beta_D$, and $\alpha\beta_E$) the dimeric precursor αC-β polypeptide and including, but not limited to, derivatives, homologues, analogues, mutants and variants thereof. Thus, the claims are drawn to screening a genus of inhibin molecules.

However, the definition of what encompasses inhibin polypeptides fails to adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera-, i.e. derivatives, homologues, analogues, mutants, and variants. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, **defined** by structure, or defined by structure in conjunction with specific

functional characteristics falling within the scope of the genus. However, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of inhibins that would distinguish the claimed inhibin from other molecules with the same biological properties. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of certain inhibins is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of inhibins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 58, 60, 62, 63, and 68 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for a mammal having prostate cancer comprising determining the amount of inhibin protein levels in both cancerous and corresponding normal prostate samples, wherein the presence of prostate cancer is verified by the *absence* of inhibin protein in the cancerous samples versus the normal samples, does not reasonably provide enablement for the broadly claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 58, 60, 62, and 63, are broadly drawn to screening for prostate cancer by determining modifications to inhibin protein levels relative to inhibin protein levels in a normal mammal. The specification teaches (page 4) that the term "modulating" means up-regulating or

down-regulating. Further, the specification teaches (page 15) that reference to "down-regulation" should be understood to include reference to the complete absence or total loss of protein and/or gene expression.

However, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to detecting up-regulating or down-regulating, and the specification only reasonably enables determining the *absence* of inhibin protein levels compared to its presence in normal prostate tissue (page 43, Example 12).

Further, there is insufficient guidance and evidence thereof for screening for a mammal having a predisposition to prostate cancer wherein modification of inhibin protein levels in said mammal relative to the inhibin protein levels in a normal mammal is indicative of said mammal being predisposed to develop prostate cancer. Neither the specification nor any art of record indicates, suggests, or teaches that down-regulation or the absence of inhibin would lead one of ordinary skill in the art to predictably determine a predisposition to prostate cancer in an otherwise normal healthy mammal. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders such as prostate cancer. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be

used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

For all of the forgoing reasons, it is concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of working examples, the nature of the invention, the state of the prior art with its recognized unpredictability and the breadth of the claims, it would require undue experimentation for one of skill in the art to practice the invention as broadly claimed.

Thus, only a method of screening for a mammal having prostate cancer comprising determining the amount of inhibin protein levels in both cancerous and corresponding normal prostate samples, wherein the presence of prostate cancer is verified by the *absence* of inhibin protein in the cancerous samples versus the normal samples, but not the full breath of the claims, meets the guidelines under 35 USC 112, 1st paragraph, scope of enablement.

Rejections Maintained:

Claims 58, 60, and 62 remain rejected and newly amended Claim 63 is rejected under 35 U.S.C. 102(b) as being anticipated by Teni *et al.* (Clinical Chemistry, Volume 35, No. 7, pages 1376-1379, 1989) for the reasons of record.

Applicants have now supplied the Gordon reference and argue that the sequence identified as β-inhibin by Seth and other was determined to be structurally identical to a sperm-coating antigen and designated as β-MSP. Applicants assert that β-MSP is also known as PIP which has no sequence homology to applicant's claimed inhibin protein. And, as indicated in Gordon, β-MSP is not believed to be an inhibin. These arguments have been carefully considered but are not found persuasive. The Gordon *et al.* reference does not specifically teach that β-MSP and PIP are the same amino acid sequence. On the contrary, the abstract states that β-MSP revealed a greater than 96% homology with β-inhibin including amino acids substitutions and a deletion. Thus, it cannot be determined if PIP is indeed not an inhibin. Further, applicants have not demonstrated an amino acid sequence for inhibin so there is no way to determine whether or not inhibin and PIP are not one in the same. Moreover, as set forth previously, the specification broadly defines the term "inhibin". This includes fragments, said fragments having the functional activity of inhibin and further includes homologues, analogs, mutants, variants and derivatives thereof (specification, page 7, lines 5+). Thus, broadly interpreted, a prostatic inhibin-like peptide (i.e. PIP) is a fragment, variant, or derivative of inhibin. It is noted that the claims do not identify any functional activity associated with the claimed inhibin molecules. Thus arguments that β-MSPs and PIPs are not inhibins (via functional experimentation) does not remove PIP (or

βMSP) from the specification's definition of what is included or excluded by the term "inhibin". Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

March 25, 2004

GARY NICKOL
PRIMARY EXAMINER